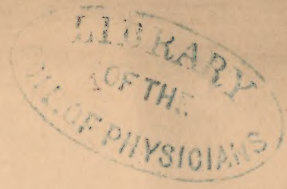


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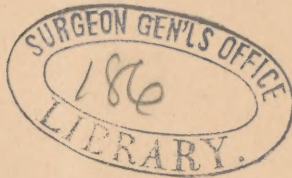
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# RECENT PROGRESS IN PHYSIOLOGY.

By H. P. BOWDITCH, M. D.

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# RECENT PROGRESS IN PHYSIOLOGY.

BY H. P. BOWDITCH, M. D.

## TRANSFUSION.

PHYSIOLOGICAL investigation within the last few years has greatly extended our knowledge of the conditions under which transfusion may be successfully performed. About two years ago, Worm Müller<sup>1</sup> studied the dependence of the arterial blood-pressure on the amount of blood circulating in the vessels. His experiments were made on dogs, and his conclusion was that three distinct grades of fullness of the blood-vessels were to be recognized:—

(1.) A grade extending from the greatest anæmia consistent with life to a condition in which the vessels contain twenty or thirty per cent. less than their normal amount of blood.<sup>2</sup> Here the arterial blood-pressure increases quite regularly from twenty-five to one hundred and thirty millimetres of mercury, in proportion to the amount of blood present in the vessels.

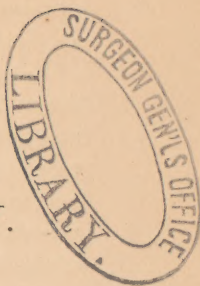
(2.) A grade extending from a condition in which the vessels contain about twenty-five per cent. less to one in which they contain from thirty to fifty per cent. more than the normal amount. Here the rise of blood-pressure with increasing volume of blood is very slight.

(3.) A grade in which the blood-volume exceeds the normal amount by more than thirty to fifty per cent. Here the blood-pressure remains unchanged, because the vessels are, according to the author, abnormally stretched.

The first grade is characterized by liability to anæmic convulsions; the third by the occurrence of vomiting. In the second grade no morbid symptoms are noticed, and this grade may therefore be regarded as representing the limits within which the vessels have the power of adapting themselves to their contents. Within this grade a sudden increase or diminution of the blood-volume causes only a very temporary increase or diminution of blood-pressure. The rapidity with which the blood-pressure returns to its normal value is so great that it cannot be accounted for by any diffusion of fluids between the blood and the tissues, and indicates that the regulating influences must be sought in the

<sup>1</sup> Arbeiten aus der physiologischen Anstalt zu Leipzig, viii. 159.

<sup>2</sup> The blood of the dog is estimated at 7.7 per cent. of the weight of the animal.





nervous system. This view is strengthened by the fact that after section of the cervical cord the phenomenon disappears.

Lesser<sup>1</sup> continued the series of experiments above described. He found that after loss of blood the blood serum becomes more watery and the coloring matter of the blood is diminished in amount. As this result follows even when both lymphatic ducts have been tied, it is evident that a *direct* diffusion of fluid from the tissues to the blood-vessels must take place. This diffusion of fluid and consequent dilution of the blood, as estimated from quantitative determinations of its solid constituents, is not sufficient to explain the observed diminution of the coloring matter of the blood, and the author is therefore led to the hypothesis that during the flow of blood from a divided vessel the first portions of blood which escape are relatively richer in globules than those which flow later, when the force of the blood-stream is diminished.

Experiments consisting in the introduction of an additional amount of blood into the vessels showed that under these circumstances a diffusion of fluid from the vessels to the tissues takes place, though the amount of this diffusion could not be accurately determined. It was found in these experiments that no morbid symptoms were produced even when the injected blood equaled in amount that which was normally present in the vessels.

It will be seen from the experiments of Worm Müller and Lesser that the limits within which the blood-volume may be varied with impunity are pretty wide ones, and that in an ordinary transfusion there can be little risk of producing a dangerous degree of plethora.

The question whether the blood of animals may be safely transfused into the human system has lately received a good deal of attention. It was generally regarded as settled in the negative, when, a few years since, the work of Gesellius<sup>2</sup> again awakened an interest in the matter. This writer maintained the harmlessness of transfusions between two different species of animals, and between animals and men. This view was based upon statistics of the operation, and upon experiments of his own performed upon dogs, lambs, and calves. His method consisted in transferring the blood by means of a short glass canula directly from an artery of one animal to a vein of another animal or of a human being. Hasse<sup>3</sup> also transfused the arterial blood of lambs directly into the veins of patients suffering from phthisis and other diseases, and considered the results upon the whole favorable. He mentions, however, as frequent results of the operation, chills and fever, and sometimes hæmaturia, or rather "hæmoglobinuria," to use the term employed by Ponfick<sup>4</sup> to indicate the presence of the coloring matter of the blood, with-

<sup>1</sup> Arbeiten aus der physiologischen Anstalt zu Leipzig, ix. 50.

<sup>2</sup> Die Transfusion des Blutes. St. Petersburg and Leipzig, 1873.

<sup>3</sup> Die Lammbhut-Transfusion beim Menschen. St. Petersburg and Leipzig, 1874.

<sup>4</sup> Virchow's Archiv, lxii. 273.



out any blood globules, in the urine. In addition to these symptoms, Fiedler and Birch-Hirschfeld<sup>1</sup> mention dyspnoea, pain in the back, vomiting, and sometimes urticaria, as the result of the direct transfusion of lamb's blood into consumptive patients. No improvement in the condition of the patients was observed.

Several fatal cases of lamb's-blood transfusion have been placed on record, but the autopsies have not thrown much light on the cause of death.<sup>2</sup> The subject has, however, been very thoroughly investigated in experiments on animals. Panum<sup>3</sup> experimented on dogs on which, previous to the transfusion, a depletion of corresponding amount had been made. He found that a transfusion of fifty-five per cent. of lamb's blood was fatal after three hours, while a transfusion of fifteen per cent. of calf's blood caused death after thirty hours. Bleeding from the wound and hæmaturia were constant symptoms. The autopsies showed hyperæmia of the kidneys, ecchymoses of the liver, and infiltration of blood into the mucous membrane of the large intestine. Ponfick<sup>4</sup> found that similar quantities (thirteen to eighteen per cent. of the normal blood-volume) produced fatal results when injected into the veins of dogs. Similar results were obtained by Mittler<sup>5</sup> in experiments on birds and mammals. He describes the kidneys as not only hyperæmic but as sometimes the seat of infarctions. Worm Müller has in a recent work<sup>6</sup> studied very carefully the effect of the transfusion of lamb's blood into dogs. He finds that a fatal result always follows the introduction into the circulation of a dog of a quantity of lamb's blood equal to twenty per cent. of the normal amount contained in the vessels. Neither a preliminary depletion of the dog nor defibrination of the lamb's blood diminishes the fatal effect of the transfusion. Capillary hæmorrhage from the wound and blood-colored urine are the principal symptoms. The autopsies show almost always great hyperæmia of the kidneys, and frequently a similar condition in the lungs, with infarctions or small extravasations, effusion of blood into the intestinal canal, and bloody exudations into the peritoneal cavity.

Ponfick<sup>7</sup> has fixed the amount of lamb's blood which can be transfused into a dog without producing bloody excretions at one and a half per cent. of the dog's blood-volume. The statement of Gesellius that four per cent. can be thus transfused is probably explained by the fact that the method employed by this observer (direct transfusion from artery to vein by a short canula) does not permit the amount of blood transfused to be accurately measured.

<sup>1</sup> Deutsches Archiv für klinische Medicin, 1874, page 545.

<sup>2</sup> Masing, St. Petersburger medicinische Zeitschrift, iv. 68.

<sup>3</sup> Virchow's Archiv, xxvii. 448.

<sup>4</sup> Virchow's Archiv, xxvii. 304.

<sup>5</sup> Wiener Sitzungsberichte, lviii., 1868.

<sup>6</sup> Transfusion und Plethora. Christiania, 1875.

<sup>7</sup> Virchow's Archiv, xxvii. 321.

It will next be of interest to consider how the above-mentioned symptoms and morbid appearances are produced. In the first place, it seems evident that the fever is not due to the transfusion of *foreign* blood as such, but to its transfusion *directly* from artery to vein; for it has been shown by Liebrecht<sup>1</sup> that fever may be produced in a dog by direct transfusion from an artery to a vein of the same animal. Here, of course, the blood-volume is unaltered, the only change being that the blood reaches the right side of the heart in greater abundance and in a less deoxidized condition than under normal circumstances. It is to a congestion of the portal system caused by this increased pressure in the venæ cavæ that the author is inclined to attribute the production of fever. He alludes in this connection to the increased size of the spleen in fever. In order to show that the fever in these cases was not traumatic, and due to the application of the ligatures, the vessels were in one experiment tied three hours before the transfusion took place. During this interval no fever occurred, but as soon as the transfusion was made the temperature in the rectum rose from 39.6° to 41.5° C.

The hæmoglobinuria implies destruction of the red globules and excretion of their coloring matter. How this takes place has been investigated by various observers. Landois,<sup>2</sup> in a series of experiments on a great variety of animals, comes to the following conclusions.

(1.) The blood-serum of many mammals dissolves the blood-globules of other mammals. Of the different sorts of serum thus far investigated, that of the dog is the most powerful in this respect, that of the rabbit the weakest.

(2.) Mammalian blood-globules have very different powers of resisting solution in the serum of other animals. The globules of the rabbit are very easily dissolved, while those of the cat and dog are very resistant.

(3.) In transfusions of foreign blood, the globules of one species are dissolved in the blood of the other. Defibrination of the transfused blood does not alter this result.

(4.) The constituents of the dissolved globules are excreted chiefly by the kidneys, occasionally also by the intestines, uterus, bronchial tubes, and into the serous cavities.

It will thus be seen that in any case of transfusion of foreign blood, the number of globules dissolved, and the consequent amount of hæmoglobinuria, will depend, first, upon the amount of blood transfused, and secondly, upon the solubility of the two sorts of blood-globules in the plasma of the blood with which they are mixed.

In a later article,<sup>3</sup> Landois follows very carefully under the micro-

<sup>1</sup> Centralblatt für die medicinischen Wissenschaften, 1874, page 580.

<sup>2</sup> Centralblatt für die medicinischen Wissenschaften, 1873, pages 883 and 897.

<sup>3</sup> Centralblatt für die medicinischen Wissenschaften, 1874, page 420.



scope the solution of blood-globules in serum of a different sort of blood. The first effect which is observed when a drop of blood is placed in foreign serum is that the globules adhere together and become spherical. They then lose their coloring matter, the globules at the circumference of the drop being first affected. Finally, nothing remains but an adherent, tenacious mass of stroma substance, in which the outlines of the single globules are at first discernible, but after a slight agitation in the surrounding fluid these outlines disappear and the whole mass is seen to consist of tenacious threads and fibres. This fibrous substance thus formed from the stroma of the blood-globules is termed by the author "stroma-fibrin," to distinguish it from the ordinary or "plasma-fibrin." Landois considers that it is this sort of fibrin which Heynsius has described<sup>1</sup> as being derived from the blood-globules.

When, by the transfusion of foreign blood, two sorts of blood are mixed together in the circulatory system, the conditions necessary for the formation of stroma-fibrin are present, and the more venous the character of the blood, the more rapidly will the stroma-fibrin be formed, for it is found that the presence of carbonic acid favors the solution of the blood-globules.<sup>2</sup> The more rapidly the transfusion of foreign blood is made, the larger and more tenacious will be the masses of stroma-fibrin formed. When stroma-fibrin has once been formed in the circulation, it may act as a foreign substance and lead to the production of plasma-fibrin. The coagulation may thus become more extensive. Even when the transfusion is made with the blood of the same species of animal, solution of blood-globules and formation of stroma-fibrin may occur when the globules of the transfused blood have lost their vitality. This may take place in consequence of exposure of the blood to too high a temperature, or of prolonged exposure to cold.

The above-mentioned observations of Landois explain the occurrence of death as observed by Naunyn<sup>3</sup> in the case of rabbits into whose veins "lake-colored" or "laky"<sup>4</sup> blood had been injected. Thrombosis of the right heart and of the pulmonary artery was found to be the cause of death in most of these cases.

These observations have been confirmed by Plósz and Györgyai,<sup>5</sup> who also noticed that the coagulation of blood withdrawn from the body may be greatly hastened by the addition of laky blood.

Similar results were obtained by Jakowicki,<sup>6</sup> who found that in whatever way blood was rendered laky (whether by repeated freezing or by

<sup>1</sup> Pflüger's Archiv, ii. 1, iii. 414, and ix. 514.

<sup>2</sup> Cf. Brown-Séquard, Journal de Physiologie, i.

<sup>3</sup> Archiv für experimentelle Pathologie, i. 1.

<sup>4</sup> That is, blood in which the coloring matter is not contained in the globules but diffused through the plasma.

<sup>5</sup> Archiv für experimentelle Pathologie, ii. 4.

<sup>6</sup> Reported in Centralblatt für die medicinischen Wissenschaften, 1875, page 376.

addition of ether or by shaking up with water), its transfusion into animals of the same species as that from which the blood was taken produced death, from the formation of coagula in the vessels and particularly hæmorrhagic infarction of the lungs. In dogs, hæmaturia was a constant and convulsions an occasional symptom. It will be seen that these symptoms and post-mortem appearances are similar to those above described as observed after the transfusion of foreign blood, and there can be no reasonable doubt that the pathology is the same in both cases. It is interesting, however, to notice that Fiedler and Birch-Hirschfeld<sup>1</sup> were unable to discover any solvent action of human serum on lamb's-blood globules or of lamb serum on human globules. As the same observers noticed hæmaturia as the result of lamb's-blood transfusion into their phthisical patients, it is probable that their failure to observe a solvent action in the mixed bloods depended upon their not having reproduced outside the body the conditions prevailing within the body which were necessary for the development of this action.

Another symptom mentioned by several observers as caused by transfusion of foreign blood is bleeding from the wound and from mucous surfaces. This is not a blood-colored exudation but a genuine hæmorrhage. The explanation of the phenomenon is not evident. It may be partly dependent on increased blood-pressure in certain vessels caused by the obstruction of neighboring channels by coagula. Worm Müller, however,<sup>2</sup> is inclined to attribute it to a weakening or solvent action of the foreign blood on the walls of the blood-vessels.

As a circumstance contributing to a fatal result in many cases of transfusion of foreign blood should be mentioned the interference with the renal functions caused by infarction of the blood-vessels, and the obstruction of the tubules by a blood-stained granular mass, as has been described by several observers. It is possible that the convulsions observed by Jakowicki<sup>3</sup> may have been due to uræmia caused in this way:

It will next be of interest to consider what becomes of the blood which is transfused into the vessels of an animal already containing a normal amount, the injected blood being from an animal of the same species. This question has been very carefully studied by Worm Müller.<sup>4</sup> He finds in the first place that, after increasing the blood-volume of a dog eighty-three per cent., about one half of the transfused blood disappears from the vessels within a few hours, and that within two to five days the blood-volume has returned to its normal amount. The different constituents of the blood do not, however, disappear with

<sup>1</sup> Deutsches Archiv für klinische Medizin, 1874.

<sup>2</sup> Transfusion und Plethora, page 115.

<sup>3</sup> See above.

<sup>4</sup> Transfusion und Plethora.



equal rapidity. If the blood of the animal is examined two or three days after the transfusion by the method of Malassez<sup>1</sup> the relative number of blood-globules is found to be greatly increased. At the same time there is found to be a considerable increase of urea in the urine. It seems evident, therefore, that of the extra blood thus injected into the vessels, the plasma is rapidly exuded and its albuminoid constituents decomposed, while the blood-globules are retained for a certain length of time unchanged. Exactly how long this increased "globular richness" can be maintained is not precisely determined, but it seems probable that it may last for several weeks.

#### INDICATIONS FOR TRANSFUSION.

Looking at the practical question of transfusion in the light of the above-described physiological investigations, Panum has recently<sup>2</sup> considered the conditions in which transfusion is indicated. Regarding the blood as a fluid tissue which does not contain at any one time a great amount of nutritive material, but which serves as a medium for transporting nutritious substances from the intestines to the tissues, he maintains that transfusion is not to be undertaken with a view of nourishing the body. He points out that of the transfused blood the blood-globules are retained in the vessels for a considerable time, and therefore do not serve as nutritive material, while the albuminoid materials of the plasma, which are really decomposed, are present in too small amount to be of any importance. He shows, too, that the daily loss of weight observed in a starving dog is increased instead of diminished by transfusion, perhaps in consequence of an increased supply of oxygen introduced by the more numerous blood-globules. The statements made by various observers that starving dogs can be kept alive by transfusions he regards as erroneous, for dogs often live four weeks without food, and it has not been claimed that they can be kept alive by transfusions for any greater length of time. In this connection it is interesting to notice the results arrived at by Tschiriew (in an article to be published in the next volume of Ludwig's *Arbeiten*), who introduced equal amounts of defibrinated blood alternately into the stomach and into the blood-vessels of a dog, and determined the effect on the excretion of urea of each of these operations. He found that, while the giving of blood as food caused the excretion of a quantity of urea containing an amount of nitrogen almost precisely equal to that of the ingested blood, the transfusion of blood caused a comparatively very small increase in the urea excretion.

The fact that the blood-globules of the transfused blood are retained for a considerable time in the blood-vessels indicates, according to

<sup>1</sup> Boston Medical and Surgical Journal, xc. 87.

<sup>2</sup> Virchow's Archiv, lxxiii. 1.

Panum, the only class of cases where transfusion can be of use, namely, those where there is a deficiency of these oxygen-carrying elements; for example, after exhausting hæmorrhages, in cases of anæmia, chlorosis, etc. Since the blood of animals (except perhaps that of apes), to say nothing of the danger attending its employment, is unable to meet the single rational indication for transfusion, namely, the deficiency of red blood-globules, its introduction into human blood-vessels should, according to Panum, be entirely abandoned.

These views of Panum are opposed by Hasse,<sup>1</sup> who maintains that an important use of the transfused blood is to supply to the glands which furnish the digestive fluids the materials which enable them to perform their functions. In a condition of chronic inanition the blood is unable to supply this material, and the digestive functions are therefore enfeebled or suspended. If, now, the glands can be once brought into action again, digestion will be resumed and the blood thus restored to its natural condition. This object can, according to Hasse, be accomplished by the transfusion of an amount of lamb's-blood too small to produce the dangers which have been described by Panum, Ponfick, and Landois. He recommends direct transfusions by means of a small canula, to avoid the introduction of too great an amount of blood at once.

Cases in which the watery constituents of the blood are deficient, as in cholera, seem to demand the transfusion not so much of blood as of any fluid which will float the blood-globules, and enable them to perform their functions. It has in fact been found by Netter<sup>2</sup> that transfusions of water are quite as beneficial as those of blood, salt solutions, etc.

As the result of all these investigations, it may be said that the transfusion of animal blood into the human circulation is attended by a certain degree of danger. Human blood, where procurable, should therefore be preferred. In regard to the question of direct or indirect transfusion, it should be borne in mind that one of the chief advantages claimed for the method of direct transfusion from vein to vein over that of injecting defibrinated blood by means of a syringe is that the blood thus transfused contains all its usual constituents. It is, however, the almost unanimous opinion of investigators of this subject that no difference in the effect, either for good or for evil, is to be found between defibrinated and undefibrinated blood. In view, therefore, of the possibility of the formation of coagula in the tubes used for direct transfusion, and the difficulty<sup>3</sup> of correctly estimating the amount transfused, the indirect method seems upon the whole preferable.

<sup>1</sup> Virchow's Archiv, lxiv. 243.

<sup>2</sup> Gazette des Hôpitaux, 1873, No. 139.

<sup>3</sup> This is reduced to a minimum by the apparatus of Aveling. See The Boston Medical and Surgical Journal, xci. 31.



In this connection is to be mentioned a method proposed by Nicolas Duranty,<sup>1</sup> for transfusing undefibrinated blood by the indirect method. Taking advantage of the fact that cold delays coagulation, he catches the blood in a cold vessel and injects it by means of a cold syringe. In a series of experiments performed on animals he found that no disagreeable symptoms followed the injection of the cold blood. Worm Müller also<sup>2</sup> mentions the fact that exposure to a temperature of from 3° to 4° C. does not act injuriously upon the red blood-globules.

As bearing upon this question of the resistance of blood-globules to low temperatures, it is interesting to notice the observations of Horvath<sup>3</sup> on hibernating animals. The temperature measured in the rectum of a marmot sleeping in an atmosphere of 2° C. was found by this observer to be the same as that of the surrounding medium.

<sup>1</sup> Gazette hebdomadaire de Médecine et de Chirurgie, 1874, No. 9.

<sup>2</sup> Transfusion und Plethora, page 61.

<sup>3</sup> Centralblatt für die medicinischen Wissenschaften, 1872, page 706.

